Remarks

Claims 34, 43, 56 and 86-114 are pending. Please cancel claims 86, 87, 92, 94, 95, 100, 106, 107 and 112 as these claims pertain to a non-elected invention. Claims 34, 43, 56, 88-91, 96-99, 105 and 108-111 have been amended. New dependent claims 115-139 have been added. Support for the amendment to claims 34, 43, 56, 88-91, 96-99 and 108-111 can be found in the specification on page 2, lines 25 and 26 as well as page 51, line 8. Amendment of claim 105 was as suggested by the Examiner. Support for new claims 115-120 and 131-139 can be found on page 2, lines 25 and 26, page 51, line 8 and the previously pending claims. Support for new claims 121-123, 125, 126, 128 and 129 can be found on page 5, lines 3-6. Support for new claims 124, 127 and 130 can be found on page 50, line 22. No new matter has been added.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

Claims 34, 43, 56, 88-91, 93, 96-99, 101-105, 108-111, 113 and 114 are rejected under 35 U.S.C. §112, first paragraph, as not being sufficiently enabled so that one skilled in the art can use the invention commensurate in scope with these claims. The Examiner maintains that the specification, while being enabling for methods relating to modulating vasodilation or vasoconstriction of cerebral blood flow with an EDG-3 receptor inhibitor (such as sphingosine or suramin), does not provide enablement for such methods in any artery with any agent that downregulates any EDG receptor. Applicants have amended the claims and subsequently traverse the rejection.

The Examiner states that the specification teaches that vasoconstriction was elicited only in cerebral vessels through the action of sphingosine-1-phosphate (S1P). Applicants respectfully disagree. Applicants have shown that vasoconstriction was observed in cerebral arteries and coronary arteries to a lesser extent. (see Examples, page 50, line 22 and Table 1). Additionally, since Applicants' discovery, other groups have also confirmed the vasoconstrictive effects of S1P in non-cerebral arteries. For instance, Bischoff et al. found that S1P induced constriction of renal and mesenteric vessels *in vitro* and reduced blood flow in the same *in vivo* (see Bischoff, A., et al., 2000. Sphingosine-1-phosphate and sphingosyl-phosphorylcholine constrict renal and mesenteric microvessels *in vitro*. Br. J. Pharmacol. 130, 1871-1877 and Bischoff, A., et al., 2000. Sphingosine-1-phosphate reduces rat renal and mesenteric blood flow *in vivo* in a pertussis toxin-sensitive manner. Br. J. Pharmacol. 130, 1878-1883). Ohmori, et al. similarly confirmed

vasoconstriction with S1P in human coronary artery smooth muscle cells (see Ohmori, T., et al., Sphingosine 1-phosphate induces contraction of coronary smooth muscle cell via S1P(2). Cardiovasc Res 2003 Apr; 58(1):170-7). The observation of lesser vasoconstriction in the non-cerebral arteries may be due to the action of S1P-phosphatase. The level of S1P-phosphatase was higher in coronary, carotid and femoral arteries than in the cerebral arteries. This indicates that under conditions where S1P-phosphatase is present, the action of S1P on EDG receptors may be reduced. However, this does not indicate that vasoconstriction is not regulated by the EDG receptors. Under different conditions in these arteries, the levels of S1P-phosphatase may be reduced and vasoconstriction (and thus vasodilation) allowed to proceed through the signaling effects of the EDG receptors. Additionally, vasoconstriction can be regulated through the EDG receptors in these arteries with other ligands or agents that act on the various proteins involved in the vasoconstrictive transduction pathway (e.g. G_q, $G_{12/13}$ or small G proteins of the Rho family).

The Examiner also reasoned that the specification teaches that the EDG-3 receptor, and not other EDG receptors, mediates the vasoconstrictive response. The Examiner references Applicants' experiments with inhibitors to specific G proteins as well as the antisense experiments provided in the specification (pages 52-53). Although these experiments show that at least EDG-3 is involved in vasoconstriction with S1P, they do not preclude the involvement of other EDG receptors. For instance, it is likely that there are differences in the transduction pathways that regulate vasoconstriction and, therefore, other proteins may be involved in the vasoconstrictive transduction pathways of the S1P-binding EDG receptors. Additionally, the antisense experiment does not conclusively rule out the involvement of the EDG-5 receptor (e.g., the turnover rate of the EDG-5 receptor may be lower than that of EDG-3, leading to the result seen in Applicants' antisense experiment).

There is also additional evidence that implicates other EDG receptors in vasoconstriction. Additional studies performed by Applicants indicate that the contractile response with S1P was significantly reduced by *Pertussis* toxin (see Salomone, S., et al., 2003. $S1P_3$ receptors mediate the potent constriction of cerebral arteries by sphingosine-1-phosphate. Eur. J. of Pharmacology 469: 125-134). This implicates the involvement of $G_{i/o}$ heterotrimeric G proteins in addition to the $G_{12/13}$ proteins implicated in previous experiments. Furthermore, there is additional evidence confirming that EDG-5 is involved in vasoconstriction induced by S1P. Ohmori et al., 2003 found that an antagonist to S1P(2) (also known as EDG-5) inhibited vasoconstriction in cardiac smooth muscle cells. Although the Examiner concluded that one of ordinary skill in the art

would expect that other EDG receptors would function differently from the EDG-3 receptor, Applicants disagree and assert that it is just as likely that one of ordinary skill in the art would expect that other S1P binding EDG receptors would function similarly to the EDG-3 receptor. The above evidence supports this assertion.

The Examiner also pointed to the fact that LPA binds to EDG-2 and -4 receptors, while S1P binds to the other EDG receptor subtypes (according to Goetzl et al., 1999). Applicants wish to clarify that the methods of the pending claims relate to the S1P-binding EDG receptors responsible for inducing vasoconstriction and, therefore, not EDG-2 and -4 which bind LPA and not S1P. In order to clarify this, Applicants have amended pending claims 34, 43 and 56 to read on the S1P-binding EDG receptors. Support for this amendment can be found on page 2, lines 25 and 26 as well as page 51, line 8.

Finally, Applicants contend that with the guidance provided in the specification as well as the level of skill in the art, one of ordinary skill is able to determine any agent that would function to downregulate S1P-binding vasoconstricting EDG receptor signaling. The standard for enablement is whether undue experimentation would be required for one of ordinary skill in the art to practice the claimed invention. To determine whether experimentation is undue, an analysis of the factors set forth in *In re Wands* is required. *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). The Examiner has recited these factors but has not analyzed each one of them in order to reach the present conclusion. One of ordinary skill in the art would need to use only routine experimentation to produce agents that can regulate such receptor signaling. These agents include agents that bind the receptors blocking their interaction with activating ligands, agents that bind the natural ligands of the receptors blocking their interaction with the receptors, agents that block the interaction of proteins involved downstream in the signal transduction pathway responsible for inducing vasoconstriction, as well as agents that modify the activating ligands (e.g., S1P-phosphatase as well as activators of S1P-phosphatase production). Because the ordinary skill in the art is high, only routine experimentation is required to produce these agents and to test them for the desired activity.

As the arguments presented by the Examiner do not support the conclusion that experimentation is undue, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, first paragraph

The Examiner has rejected claim 104 under 35 U.S.C. §112, first paragraph as containing subject matter that was not "described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention."

The Examiner maintains that the claim does not require the neuroprotective agent to possess a specific activity, particular structure or other distinguishing feature. Therefore, according to the Examiner, the scope of the claim is broad enough to encompass any agent as long as it functions to protect the nervous system as well as agents that are yet to be discovered that serve this purpose. The Examiner concludes that because no structural or functional requirements, identifying characteristics or specific examples are provided, the specification does not meet the written description requirement.

Applicants respectfully disagree with the Examiner's rejection of the claim. The Applicants maintain that the term "neuroprotective agent" is a term of art such that one of ordinary skill in the art would recognize that Applicants had possession of the claimed invention. A simple search of the PubMed database alone for the term "neuroprotective agents" found more than 21,000 articles reciting this term. Examples of compounds recited in these articles include, *inter alia*, estrogen, progesterone, lithium, minocycline, and experimental agents such as clomethiazole, AR-R15896AR and NXY-059.

In addition, the Examiner's ability to define the term neuroprotective agent speaks to the unambiguousness of the term. The definition provided by the Examiner proves that the term is understood and that one of ordinary skill in the art would know what agents are encompassed therein. Furthermore, the definition of neuroprotective agents provided by the Examiner (i.e., that they function to protect the nervous system) illustrates that the term alone is sufficient to describe the functional requirement of these agents.

Therefore, as this term is understood in the art, Applicants respectfully request the Examiner reconsider and withdraw the rejection of claim 104 under 35 USC §112, first paragraph.

Rejection of Claims Under 35 U.S.C. §112, second paragraph

Claims 104 and 105 are rejected under 35 U.S.C. §112, second paragraph for failing to "particularly point out and distinctly claim the subject matter which applicants regard as the invention."

Claim 104 recites the term "neuroprotective." The Examiner maintains that this term is indefinite because neither the art nor the specification provides an unambiguous definition for this term.

Applicants, however, respectfully disagree. As argued above, it is clear that the term is understood as evidenced by the common usage by those of ordinary skill in the art as well as the Examiner's own admission. Applicants therefore assert that the term is not indefinite. One of skill in the art would understand the second agents encompassed by claim 104.

Claim 105 recites the term "TPA". For clarity, Applicants have amended this claim as suggested by the Examiner.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, second paragraph.

Rejection of Claims - Minor Informalities

The Examiner has rejected claims 90, 97, 104 and 109 for reciting unelected species. The Applicants want to bring to the Examiner's attention that the recitation of claim 90 in terms of this rejection is incorrect. Because of the renumbering of the claims, the appropriate claim is claim 89 rather than 90. Claims 89, 97 and 109 recite unelected EDG receptor inhibitors, and claim 104 recites unelected second agents.

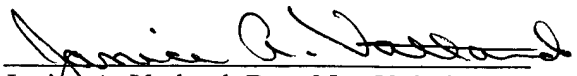
Applicants however traverse the rejection of these claims. Claims 90, 97, 104 and 109 encompass unelected species. These non-elected species are simply withdrawn from consideration and are thus not currently being examined; however they have not been deleted from these claims because under 37 C.F.R. §1.141 "upon the allowance of a generic claim, applicant will be entitled to consideration of the claims to additional species which are written in dependent form or otherwise include all of the limitations of an allowed generic claim".

Accordingly, since these species elections were required and made for examination purposes only, Applicants are not obligated to amend the claims that recite as yet unexamined species, just as they would not be required to cancel such claims. Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Summary

It is believed that all of the pending claims are in condition for allowance. If the Examiner has any questions or comments, he is encouraged to contact Applicants' representative at the number listed below.

Respectfully Submitted,



Janice A. Vatland, Reg. No. 52,318
WOLF, GREENFIELD & SACKS, P.C.
600 Atlantic Avenue
Boston, MA 02210-2211
(617)720-3500

Docket No.: M00765.70035.US
Date: June \\, 2003
X06.11.03